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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/761,209	01/16/2001	James E. Hildreth	JHU1290-7	5480

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GRAY CARY WARE & FREIDENRICH LLP  
Suite 1100  
4365 Executive Drive  
San Diego, CA 92121-2189

[REDACTED] EXAMINER

NAVARRO, ALBERT MARK

[REDACTED] ART UNIT

[REDACTED] PAPER NUMBER

1645

DATE MAILED: 03/27/2003

(D)

Please find below and/or attached an Office communication concerning this application or proceeding.

<b>Advisory Action</b>	Application No. <b>09/761,209</b>	Applicant(s) <b>Hildreth</b>
	Examiner <b>Mark Navarro</b>	Art Unit <b>1645</b>

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

THE REPLY FILED Feb 25, 2002 FAILS TO PLACE THIS APPLICATION IN CONDITION FOR ALLOWANCE. Therefore, further action by the applicant is required to avoid the abandonment of this application. A proper reply to a final rejection under 37 CFR 1.113 may only be either: (1) a timely filed amendment which places the application in condition for allowance; (2) a timely filed Notice of Appeal (with appeal fee); or (3) a timely filed Request for Continued Examination (RCE) in compliance with 37 CFR 1.114.

**THE PERIOD FOR REPLY [check only a) or b])**

- a)  The period for reply expires 4 months from the mailing date of the final rejection.
- b)  The period for reply expires on: (1) the mailing date of this Advisory Action, or (2) the date set forth in the final rejection, whichever is later. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of the final rejection. ONLY CHECK THIS BOX WHEN THE FIRST REPLY WAS FILED WITHIN TWO MONTHS OF THE FINAL REJECTION. See MPEP 706.07(f).

Extensions of time may be obtained under 37 CFR 1.136(a). The date on which the petition under 37 CFR 1.136(a) and the appropriate extension fee have been filed is the date for purposes of determining the period of extension and the corresponding amount of the fee. The appropriate extension fee under 37 CFR 1.17(a) is calculated from: (1) the expiration date of the shortened statutory period for reply originally set in the final Office action; or (2) as set forth in (b) above, if checked. Any reply received by the Office later than three months after the mailing date of the final rejection, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

1.  A Notice of Appeal was filed on \_\_\_\_\_ . Appellant's Brief must be filed within the period set forth in 37 CFR 1.192(a), or any extension thereof (37 CFR 1.191(d)), to avoid dismissal of the appeal.
2.  The proposed amendment(s) will not be entered because:
  - (a)  they raise new issues that would require further consideration and/or search (see NOTE below);
  - (b)  they raise the issue of new matter (see NOTE below);
  - (c)  they are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal; and/or
  - (d)  they present additional claims without canceling a corresponding number of finally rejected claims.

NOTE: \_\_\_\_\_

3.  Applicant's reply has overcome the following rejection(s):
   
\_\_\_\_\_  
\_\_\_\_\_
4.  Newly proposed or amended claim(s) \_\_\_\_\_ would be allowable if submitted in a separate, timely filed amendment canceling the non-allowable claim(s).
5.  The a)  affidavit, b)  exhibit, or c)  request for reconsideration has been considered but does NOT place the application in condition for allowance because:
   
See attached
  
\_\_\_\_\_  
\_\_\_\_\_
6.  The affidavit or exhibit will NOT be considered because it is not directed SOLELY to issues which were newly raised by the Examiner in the final rejection.
7.  For purposes of Appeal, the proposed amendment(s) a)  will not be entered or b)  will be entered and an explanation of how the new or amended claims would be rejected is provided below or appended.

The status of the claim(s) is (or will be) as follows:

Claim(s) allowed: \_\_\_\_\_

Claim(s) objected to: \_\_\_\_\_

Claim(s) rejected: 8, 9, 11-17, and 24

Claim(s) withdrawn from consideration: \_\_\_\_\_

8.  The proposed drawing correction filed on \_\_\_\_\_ is a)  approved or b)  disapproved by the Examiner.
9.  Note the attached Information Disclosure Statement(s) (PTO-1449) Paper No(s). \_\_\_\_\_
10.  Other: \_\_\_\_\_

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### **ADVISORY ACTION**

Applicant's amendment filed February 25, 2003 (Paper Number 11) has been received and entered. Claim 10 has been canceled and new claim 24 has been added, consequently claims 8-9, 11-17 and 24 are pending in the instant application.

#### ***Claim Rejections - 35 USC § 112***

1. The rejection of claim 10 under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention is maintained as applied to newly added claim 24.

Applicant's are asserting that the standard for enablement is not whether a method corresponding to the claimed invention has been demonstrated, instead the test for enablement is whether undue experimentation would have been required for one skilled in the art to practice the claimed invention. (*In re Wands*, 8 U.S.P.Q.2d 1400 (Fed. Cir. 1988)). Applicant's further assert that the specification sets forth of examples demonstrating that administration of an antibody capable of suppressing intercellular leukocyte adhesion, wherein the antibody binds to an epitope on the leukocyte adhesion receptor β-chain, can effectively inhibit syncitium formation and inhibit HIV gp120 binding by H52. Applicant's assert that in view of such a disclosure the skilled artisan would reasonably believe that the aforementioned inhibitory action can be predictive of results in

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vivo. Applicant's further point to Exhibits A-C to support the position that those skilled in the art believe that passive immunotherapy can be useful for treating AIDS.

Applicant's arguments have been fully considered but are not found to be fully persuasive.

The legal considerations that govern enablement determinations pertaining to undue experimentation are disclosed in *In re Wands*, 8 U.S.P.Q.2d 1400 (C.A.F.C. 1988). The courts concluded that several factual inquiries should be considered when making such assessments including the quantity of experimentation necessary, the amount of direction or guidance presented, the presence or absence of working examples, the nature of the invention, the state of the prior art, the relative skill of those of the art and the breadth of the claims. *In re Rainer*, 52 C.C.P.A. 1593, 347 F.2d 574, 146 U.S.P.Q. 218 (1965). The disclosure fails to provide any guidance pertaining to a number of these considerations as follows:

- 1) The disclosure fails to provide any working embodiments that meet the claimed limitations.
- 2) The prior art describes a number of concerns and failures pertaining to the development of immunotherapy for the amelioration of HIV. Fahey et al (Clin. Exp. Immunol. Vol. 88, pp 1-5, 1992) in which a summary of the results obtained in trials using numerous different types of immune-based therapies have not achieved success. (See table 1).

The disclosure fails to provide any guidance pertaining to these caveats. Accordingly, when all the aforementioned factors are considered *in toto*, it would clearly require undue experimentation from the skilled artisan to practice the claimed invention.

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Applicant's further point to Exhibits A-C to support the position that those skilled in the art believe that passive immunotherapy can be useful for treating AIDS. However, the exhibits cited by Applicants are currently ongoing, whereas the filing date of the instant application is June 1989 and therefore the exhibits are not an enabling disclosure at the time of the instant application. (See *In re Glass* 181 USPQ 31 (CCPA 1974). Furthermore, Applicant's cited Exhibit B is merely a study to determine the safety of a human monoclonal antibody. No demonstration of the amelioration of HIV is presented. Furthermore, Exhibit C is a study of the combination of immunotherapy and anti retroviral therapy. This is simply not commensurate in scope with Applicants claims which recite solely immunotherapy. As set forth previously, Fahey et al have characterized the lack of efficacy of immunotherapy in ameliorating HIV.

The claim is directed to methods of ameliorating an immune response mediated disorder in an animal wherein the disorder is AIDS, autoimmune disease, and graft rejection.

Applicant's specification contains insufficient guidance to one of skill in the art for the treatment of AIDS, autoimmune disease and graft rejection. The specification provides no description of critical parameters for administering antibodies in order to achieve a desired therapeutic outcome. General protocols for effective antibody-based treatment of AIDS, autoimmune disease, and graft rejection have not yet been established in the art. The specification does not describe what, if any, clinical changes or benefits are manifested as the result of monoclonal antibody-mediated individuals suffering from AIDS, autoimmune diseases or graft

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rejection such that one of skill in the art could determine the efficacy of the claimed invention. Undue experimentation would be required of one of skill in the art to practice the claimed methods relying only on the teachings of the instant specification for guidance in view of the current state of the art to which the invention pertains.

The obstacles to the development of therapeutic approaches with regard to the treatment of HIV-1 infection in humans are well documented in the scientific literature. These obstacles include the fact that the modes of viral transmission include virus-infected mononuclear cells which pass the infecting virus to other cells in a covert form, as well as via free virus transmission, the existence of a latent form of the virus, the ability of the HIV-1 virus to hide in the central nervous system where blood cells and neutralizing agents carried by the blood cannot reach the retrovirus due to the blood-brain barrier, and the complexity and variation of the elaboration of the disease. The status of immunobased therapies in HIV infection and AIDS is summarized in a review article by Fahey *et al* (Clin. Exp. Immunol. Vol 88, pp 1-5, 1992), cited of interest, Fahey *et al* teach that clinical benefit in trials using different approaches to immune-based therapies have not achieved a great deal of success. Table 1 on page 2 summarizes the results obtained in trials using numerous different types of immune-based therapies and teaches that antibody-based therapies involving the administration of immune serum gamma globulin or murine anti-gp160 monoclonal antibodies did not achieve clinical change or benefit. In view of the lack of working examples, and the lack of success which has been achieved to date in the use of immune-based therapies in general, and of antibody-based therapies in particular, for therapy of HIV-1 infection,

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one of skill in the art would be forced into undue experimentation to practice the broadly claimed invention.

For reasons of record in Paper Number 9, as well as the reasons set forth above this rejection is maintained.

***Claim Rejections - 35 USC § 102***

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless --

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

(e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

2. The rejection of claims 8-9, 11, and 13-15 under 35 U.S.C. 102(e) as being anticipated by Arfors is maintained.

Applicant's are asserting that Arfors do not teach or suggest an immune response mediated disorder or of ameliorating an immune response mediated disorder.

Applicant's arguments have been fully considered but are not found to be fully persuasive.

Applicant's arguments are not found to be fully persuasive in view of the teachings of Arfors.

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Arfors disclose of administering an antibody which binds to an epitope on the leukocyte adhesion receptor  $\beta$ -chain in order to prevent ischemia/reperfusion-induced tissue damage. (See column 2). Ischemia leads to necrosis, thus Arfors is ameliorating an immune response mediated disorder in that necrosis involves an immune response (inflammation) at the site of injury.

Administration of the antibody to prevent necrosis or limit the amount of necrosis which takes place is thus deemed to be the amelioration of an immune response mediated disorder.

Applicant's have further attached Exhibit D showing that ischemia/reperfusion injury is an activated oxygen species mediated disorder, not an immune response mediated disorder. However, while this point is agreed upon, it has no bearing on the fact that ischemia results in necrosis. Necrosis leads to an immune response. Consequently, the administration of anti LAR- $\beta$  chain specific monoclonal antibodies to a mammal suffering from ischemia is ameliorating the immune response mediated disorder.

The claims are directed to a method of ameliorating an immune response mediated disorder in an animal which comprises: administering to the animal a therapeutically effective amount of an antibody, capable of suppressing intercellular leukocyte adhesion, wherein the antibody binds to an epitope on the leukocyte adhesion receptor  $\beta$ -chain.

Arfors (U.S. Patent Number 4,797,277) disclose of a method for treating mammalian organs suffering from ischemia in order to prevent ischemia/reperfusion-induced tissue damage, which involves administering anti LAR- $\beta$  chain-specific monoclonal antibody 60.3. (See column

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- 2). The examples describe parenteral administration at a dose within the range specified in claim 15.

For reasons of record in Paper Number 9, as well as the reasons set forth above this rejection is maintained.

3. The rejection of claim 8 under 35 U.S.C. 102(b) as being anticipated by Vedder *et al* is maintained.

Applicant's assertions are the same as those set forth above in paragraph 2, and have been addressed accordingly above in paragraph 2.

Vedder *et al* (J. Clin. Invest. Vol. 81, pp 939-944, 1988) disclose of a method for reducing leukocyte-mediated organ injury by administering anti-CD18 monoclonal antibody 60.3.

#### ***Claim Rejections - 35 USC § 103***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

4. The rejection of claims 8-9, 11 and 13-15 under 35 U.S.C. 103(a) as being unpatentable over Arfors or Vedder *et al* in view of Springer *et al* is maintained.

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Applicant's assertions are essentially the same as those set forth above in paragraph 2, and have been addressed accordingly above in paragraph 2.

Arfors and Vedder *et al* each teach that anti-CD18 monoclonal antibodies such as 60.3 inhibit leukocyte adherence functions and inhibit ischemia-reperfusion injury and speculate that these findings may be relevant to the therapy of many clinical disorders that result from ischemia and reperfusion including organ transplantation.

Neither Arfors or Vedder *et al* teach of LFA-1 or proteins capable of competing for receptors and of inhibiting cell to cell binding.

Springer *et al* (WO 88/06592) teach that the administration of LFA-1 or proteins capable of competing for receptors and of inhibiting cell to cell binding were recognized to have potential applicability for treatment of autoimmune diseases and graft rejection. (See page 12).

It would have been *prima facie* obvious to combine the teachings of the cited prior art and to administer anti-CD18 monoclonal antibodies such as Mab 60.3 which had been shown to inhibit cell adhesion, for the purpose of treating autoimmune diseases and graft rejection. One of ordinary skill in the art would have been motivated to do so in view of the teaching of Springer *et al* and Vedder *et al* as previously characterized.

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5. Claims 11-12 are rejected under 35 U.S.C. 103(a) as being unpatentable over Arfors, Vedder *et al* and Springer *et al* as applied to claims 8-9, 11 and 13-15 above, and further in view of Hildreth *et al*.

Applicant's assertions are essentially the same as those set forth above in paragraph 2, and have been addressed accordingly above in paragraph 2. Applicant's further assert that there is no motivation to combine the references in view that Vedder et al are not referring to an immunologic based rejection of an organ transplant but, instead, are describing injury that can occur upon reperfusion of the transplanted organ.

Applicant's are respectfully directed to the claim language which recites a method of ameliorating an immune response mediated disorder in an animal. As set forth above, ischemia of the organ can lead to necrosis of the tissue, which in turn results in an immune response (inflammation) at that site. It is this "immune disorder" which is being treated by the combination of the references.

Arfors, Vedder *et al* and Springer *et al* do not teach of the monoclonal antibody produced by ATCC HB X.

Hildreth *et al* (J. Immunology Vol. 134 pp 3272-3280, 1985) teach of the monoclonal antibody H52, which is the same antibody produced by the hybridoma cell line ATCC HB X. (Specification page 5).

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It would have been *prima facie* obvious to substitute H52 into the methods suggested by the combined teachings of Arfors, Vedders *et al* and Springer *et al*. One of ordinary skill would have been motivated to do so in view of the teaching of Hildreth *et al* that Mab H52 had been shown to inhibit all T cell functions tested in a manner similar to the prior art Mab 60.3 which had been shown to be effective for inhibiting ischemia/reperfusion injury.

6. Claims 16-17 are rejected under 35 U.S.C. 103(a) as being unpatentable over Arfors, Vedder *et al* and Springer *et al* as applied to claims 8-9, 11 and 13-15 above, and further in view of Pastan *et al*.

Arfors, Vedder *et al* and Springer *et al* do not teach of monoclonal antibodies labeled with a radioisotope, drug, lectin, or a toxin.

Applicant's assertions are essentially the same as those set forth above in paragraph 2, and have been addressed accordingly above in paragraph 2.

Pastan *et al* (Cell Vol. 47, pp 641-648, 1986) teach that the concept of using immunotoxins for the treatment of autoimmune disease, in autologous bone marrow transplantation and to improve organ graft survival. (See pages 645-6).

It would have been *prima facie* obvious to combine the teachings of the cited prior art and to produce conjugates comprising anti-LAR- $\beta$  chain specific monoclonal antibodies and cytotoxic moieties and to use such conjugates in methods for treating autoimmune diseases and organ

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transplantation. One of ordinary skill in the art would have been motivated to do so in view of the combined teachings of Pastan *et al*, Arfors *et al*, Vedder *et al*, and Springer *et al* as previously discussed.

***Double Patenting***

7. The rejection of claims 8-17 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-7 of U.S. Patent No. 5,888,508 is maintained.

It is noted that Applicant's have indicated a willingness to file a terminal disclaimer upon the indication of allowable subject matter. However until a terminal disclaimer is made of record this rejection is maintained.

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Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist, whose telephone number is (703) 308-0196.

Papers related to this application may be submitted to Group 1645 by facsimile transmission. Papers should be faxed to Group 1645 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the official Gazette 1096 OG 30 (November 15, 1989). The CMI Fax Center number is (703) 308-4242.



Mark Navarro

Primary Examiner

March 23, 2003